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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/837,217	04/19/2001	Chia Ning (Sophia) Chang	01779784	6921

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 01/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/837,217	CHANG, CHIA NING (SOPHIA)	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 10/20/05 has been entered.

Amended claims 1-6, 8 and 11-14 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The New Matter rejection is withdrawn in light of Applicant's amendment.

Claim Objections

Claim 8 is objected to because of the term "50 x 10^6 per ml". It appears that the term - - cells - - in front of the term "50 x 10^6 " is missing. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Amended claims 1-6, 8 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of enhancing new bone formation in a subject, comprising:

a) obtaining a plurality of bone marrow stromal cells (MSCs) from the subject;

b) transducing the MSCs of step a) with a replication-defective adenovirus vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter to generate BMP-2 protein producing MSCs;

c) applying a biodegradable plate to a site requiring new bone formation on the subject; and

c) applying a composition comprising the BMP-2 protein producing MSCs and a pharmaceutically acceptable polymer to the site,

such that new bone formation is enhanced;

and a pharmaceutical composition for application at a biodegradable plate-containing site requiring new bone formation in a subject, said composition comprising a plurality of bone marrow stromal cells transduced *in vitro* with a replication-defective adenovirus vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter;

does not reasonably provide enablement for a method of enhancing cartilage formation in a subject; **or** a method of enhancing new bone using a plurality of bone marrow stromal cells transduced *in vitro* with any other replication-defective viral vectors expressing BMP-2; **or** a pharmaceutical composition comprising a plurality of bone marrow stromal cells (MSCs) isolated from a subject, wherein the MSCs comprise any other replication-defective viral vectors expressing BMP-2; **or** a pharmaceutical composition for application at a biodegradable plate-containing site requiring new cartilage formation in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons already set forth in the previous Office Action mailed 1/29/04 (pages 4-9).

Response to Arguments

Applicant's arguments related to the issue on the formation of new cartilage by the presently claimed invention in the above rejection in the Amendment filed 06/01/04 have been fully considered, but they are not found persuasive.

Applicant argues basically that at the time of Applicant's invention the expression of BMP-2 in pluripotent stem cells (such as bone marrow stromal cells) can induce the cells to differentiate into cell types other than osteoblasts, e.g., cartilage and connective tissue, as evidenced by examples 1, 4, 11 and 15 of Moutsatsos et al. (WO 99/11664). Therefore, the ordinary skilled artisan would be able to enhance the formation of cartilage or connective tissue as well as bone without undue experimentation.

With respect to example 4 using the 10T fibroblast cells, there is no relevance between the ability for these cells to make cartilage with the bone marrow stromal cells transduced *in vitro* with a replication-deficient viral vector comprising a DNA sequence encoding BMP-2. Moreover, it is also noted that the 10T fibroblast cells were also transformed with DNA encoding parathyroid hormone receptor. Where is the teaching in the present application as filed that Applicant also contemplate to transduce the genetically modified bone marrow stromal cells with any vector encoding a parathyroid hormone receptor?

With respect to other examples 1, 11 and 15 of the Moutsatsos reference, although C3H10T1/2 cells expressing recombinant BMP-2 are capable of forming cartilage *in vivo*, it is unclear whether the genetically modified mouse cell line of Moutsatso et al. is a reasonable representative for a bone marrow stromal cell

population transduced *in vitro* with a replication-deficient viral vector comprising a DNA sequence encoding BMP-2 for the present invention, and that its differentiation behavior *in vivo* is the same as the claimed genetically modified bone marrow stromal cells. It is also noted that that the transplanted C.9 cells are transduced with a recombinant retrovirus encoding β-galactosidase in conjunction with a vector (it is not clear which vectors) expressing BMP-2 under the control of a Tet inducible promoter. Furthermore, apart from the Moutsatsos reference, **the exemplification of the present disclosure as well as the teachings of Riew et al. (Calcif. Tissue Int. 63:367-360, 1998), Lou et al. (J. Orthopaedic Research 17:43-50, 1999), and Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001)** demonstrate that adenovirus-mediated human BMP-2 gene transfer induces mesenchymal progenitor C3H/10T cells and mesenchymal stem cells to proliferate and differentiate into osteoblast phenotype that **result only in induced bone formation *in vivo***.

The examiner notes that Applicant fails to address the enablement issue on the use of other recombinant replication-deficient viral vectors other than the recombinant replication-deficient adenoviral vector given in the scope of enablement.

Thus, in light of **the totality of the prior art at the filing date of the present application**, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 102

Amended claims 1-2, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Moutsatsos et al. (WO 99/11664) for the same reasons already set forth in the previous Office Action mailed 5/13/03 (pages 3-4).

Amended claims 1-2, 4, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Riew et al. (Calcif. Tissue Int. 63:357-360, 1998) as evidenced by Caplan et al. (U.S. 5,855,619) for the same reasons already set forth in the previous Office Action mailed 5/13/03 (pages 4-5).

Amended claims 1-2, 4, 11 and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng et al. (Calcif. Tissue Int. 68:87-94, 2001) as evidenced by Caplan et al. (U.S. Patent No. 5,855,619) for the same reasons already set forth in the previous Office Action mailed 5/13/03 (pages 5-6).

Response to Arguments

Applicant's arguments related to the above rejections in the Amendment filed on 06/01/04 have been fully considered, but they are not found persuasive.

Applicant argues mainly that none of Moutsatsos et al., Rieve et al., Cheng et al. or Caplan et al teach or suggest a pharmaceutical composition for application at a biodegradable plate-containing site requiring new bone or cartilage formation in a subject. Therefore, these references do not anticipate the instant claims.

Please note that the intended use for a composition claim is not given any patentable weight in light of the prior art, for this instance the pharmaceutical composition is intended to apply at a biodegradable plate-containing site. The compositions taught by Moutsatsos et al. (WO 99/11664), Riew et al. (Calcifi. Tissue Int. 63:357-360, 1998) and Cheng et al. (Calcif. Tissue Int. 68:87-94, 2004) are indistinguishable from the pharmaceutical composition as claimed because they contain the same components. It should also be noted that the presently claimed composition only requires a plurality of bone marrow stromal cells isolated from a subject, wherein the MSCs comprise a replication-deficient viral vector comprising a DNA sequence encoding BMP-2 operably linked to a promoter, and a pharmaceutically acceptable polymer.

Accordingly, the rejections are maintained for the reasons set forth above.

Claim Rejections - 35 USC § 103

Claims 5-6 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moutsatsos et al. (WO99/11664; Cited previously) in view of Kadiyala et al. (US 6,541,024). ***This is a new ground of rejection.***

With respect to the enabled scope, Moutsatsos et al. disclose the preparation of bone marrow stromal cells transformed with a recombinant replication-deficient adenovirus vector (e.g., E1 deleted; E1, E3, E4 deleted recombinant adenoviruses) expressing one or more bone morphogenetic proteins that include human BMP-2 for regeneration of bone formation *in vivo* (see Summary of the invention and at least

example 14, pages 41-50). Moutsatsos et al. also teach that the recombinant cells can be administered in combination with an appropriate matrix for supporting the composition, and this matrix can be in the form of biocompatible matrix biomaterials (a pharmaceutically acceptable polymer) including polylactic acid, polyanhydrides, calcium sulfate, bone, dermal collagen, hydroxyappatite, aluminates, pure proteins or extracellular matrix components and others (line 32 on page 6 continues to line 27 on page 7). Furthermore, Moutsatsos et al. teach that their delivery system for rhBMP-2 can be applied locally or regionally (see examples 13-14; particularly page 41, lines 15-17 and line 34 of page 45 continues to line 2 of page 46).

Moutsatsos et al do not teach specifically a method for enhancing bone formation in a subject comprising a step of applying a biodegradable plate to a site requiring new bone formation.

However, at the effective filing date of the present application Kadiyala et al already teach a method for augmenting bone formation using isolated mesenchymal stem cells with a ceramic material or matrix in the presence of fixation devices such as polyethylene fixation plate (a biodegradable plate) or a SynthesR 8-hole lengthening plate which are internally placed and secured (see abstract; col. 4, lines 45-47; col. 11, lines 24-29; col. 20, lines 2-4; col. 22, lines 40-45).

Accordingly, it would have been obvious for an ordinary skill artisan to modify the method taught by Moutsatsos et al. by also applying a biodegradable fixation plate at a site requiring new bone formation in a subject in light of the teachings of Kadiyala et al.

An ordinary skilled artisan would have been motivated to make the above modification because the use of a biodegradable fixation plate at an injured bone area is for stabilizing during the healing process and it is routine used in a bone repair operation as taught in the exemplifications of Kadiyala et al.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Moutsatsos et al. and Kadiyala et al, coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Moutsatsos et al. (WO99/11664) in view of Kadiyala et al. (US 6,541,024) as applied to claims 5-6 and 12 above, and further in view of Tschakaloff (US 5,290,281). ***This is a new ground of rejection.***

The teachings of Moutsatsos et al. and Kadiyala et al. have been discussed above. However, none of the references teaches specifically the use a biodegradable plate comprising poly(lactic acid).

However at the filing date of the present application Tschakaloff already taught the use of body absorbable, bodily tissue fixation plates made up of materials such as polylactide, polyglycolides, polycaprolactane, poly(orthoesters) and the like which possess favorable *in vivo* strength and absorption characteristics for fixating fractured or

severed bones (see at least col. 4, lines 61-66; col. 9, line 62 continues to line 4 of col. 10).

Accordingly, it would have been obvious for an ordinary skill artisan to further modify the method of Moutsatsos et al. and Kadiyala et al by using a biodegradable fixation plate comprising poly(lactic acid) or polylactides in light of the teachings of Tschakaloff.

An ordinary skilled artisan would have been motivated to make the above modification because Tschakaloff teaches that a fixation plate made up of polylactides, polyglycolides, polycaprolactane, poly(orthoesters) or the like possesses favorable *in vivo* strength and absorption characteristics for fixating fractured or severed bones to promote rapid and beneficial healing of the treated bones.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Moutsatsos et al., Kadiyala et al. and Tschakaloff, coupled with a high level of skills of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Celine Qian, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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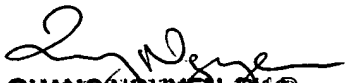

QUANG NGUYEN, PH.D.
PATENT EXAMINER